How to prevent postextubation respiratory failure

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Purpose of review
Postextubation respiratory support treatment approaches, indications, and subgroups of patients with different responses to those therapies are rapidly changing. Planning optimal therapy in terms of choosing devices, timing of application and selecting settings with the goal of minimizing extubation failure is becoming a challenge. This review aims to analyze all the available evidence from a clinical point of view, trying to facilitate decision making at the bedside.

Recent findings
There is evidence for high flow nasal cannula support in patients at low risk of extubation failure.
Noninvasive ventilation based strategies should be prioritized in patients at very high risk, who are obese or are hypercapnic at the end of a spontaneous breathing trial. Patients not included in the previous groups merit a tailored decision based on more variables.
Optimizing the timing of therapy can include facilitation of extubation by transitioning to noninvasive respiratory support or prolonging a planned preventive therapy according to clinical condition.

Summary
Planning postextubatin respiratory support must consider the risk for failing and the presence of some clinical conditions favoring noninvasive ventilation.
Extubation can be safely accelerated by modifying screening criteria and spontaneous breathing trial settings, but there is room to increase the role of postextubation noninvasive respiratory support for this indication, always keeping in mind the dangers of delaying a needed intubation.

Keywords
extubation failure, model, outcome, prediction, reintubation, weaning

INTRODUCTION

The process of liberation from invasive mechanical ventilation (MV) starts between the time when a screening test indicates that the illness precipitating the intubation is sufficiently stabilized and the first extubation attempt, and lasts until the patient can no longer be considered reintubated in case of respiratory deterioration after extubation [1,2▪▪,3]. Extubation has been traditionally understood as a milestone in this process, but increasing evidence on preextubation management and postextubation therapy has relocated its position in the middle of the entire weaning process.

This process of liberation includes four different phases that cannot be split into pieces: general clinical management during the full ventilatory support period including sedation and the evaluation of the risk for failing, and the other three that should be tailored according to the screening test to initiate the weaning period, a confirmatory test or spontaneous breathing trial (SBT) leading to extubation in patients succeeding the SBT, and postextubation management.

Noninvasive respiratory support after extubation can be used not only to prevent postextubation respiratory failure and reintubation, but also to treat mild cases of postextubation respiratory failure. It can also be used to accelerate the weaning process, shortening the duration of invasive MV and reducing its related complications. Postextubation respiratory failure is an intermediate step between extubation and reintubation only in some patients, as reintubations secondary to nonrespiratory reasons and airway complications, accounting for up

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KEY POINTS

- Postextubation respiratory support strategies should be planned according to the following subgroups: humidified noninvasive ventilation (NIV) should be selected in patients at very high risk or obese patients at intermediate risk for hypoxemic failure; any NIV based strategy could be used in patients at high risk including obese, and those hypercapnic at the end of the spontaneous breathing trial (SBT); patients at intermediate risk could receive high flow nasal cannula (HFNC) or any NIV based strategy according to other customized parameters; those at low risk should receive HFNC.
- Prolonging a planned fixed preventive therapy or prolonging noninvasive support in response to changes in clinical conditions can be useful to optimize the prevention strategy and reduce the reintubation rate.
- Extubating patients without or after failing a SBT generates clinical uncertainty. An accelerated extubation can be achieved by using earlier screening tests and easier SBTs in selected groups and then providing adequate postextubation noninvasive support.

to 43% of reintubations, do not necessarily develop respiratory failure and derive no clear benefit from postextubation respiratory support [4]. In addition, with appropriate management, postextubation respiratory failure does not necessarily lead to reintubation.

POSTEXTUBATION RESPIRATORY SUPPORT ACCORDING TO RISK FOR FAILING EXTUBATION

Planning postextubation respiratory support aims to prevent postextubation respiratory failure and reintubation according to the predicted risk for failing extubation (see Table 1).

Predicting extubation failure remains a challenge. Traditional definitions of high risk for extubation failure classify as high risk those patients with at least one high risk factor included in any of the available models. The primary aim of clinical risk models is to detect at the bedside most patients at risk, because failure to recognize patients at risk reduces use of preventive techniques and can increase the reintubation rate. On the other hand, overuse of prevention does not have adverse clinical consequences because it has not been related to worse outcomes in clinical trials, mainly delayed reintubation [8,9▪]. There are two main approaches: a pragmatic 3-factor model, including age and most relevant comorbidities (e.g., chronic lung and heart diseases) [8,9▪], with the threat of under-classification, and a time consuming 11-factors model, including age, comorbidities integrated in the Charlson index and at least moderate chronic obstructive pulmonary disease (COPD), characteristics of acute phase critical illness (e.g., prolonged MV, acute heart failure) and the clinical condition at the time of extubation (e.g., risk factors for airway failure, APACHE II, hypercapnia at the end of the SBT) [10,11], with the threat of over-classification.

These models and an intermediate 4-factor model including age, chronic heart and lung diseases and prolonged MV have been recently analyzed and compared. The 3-factor showed a very low diagnostic accuracy while the 4- and 11-factor models showed a similar low accuracy *(unpublished data)*.

Determining the risk for failing extubation became the cornerstone of the indication for postextubation respiratory support after the initial studies [16]. However, the increasing armamentarium with different physiological mechanisms, tolerance by patients and the difficulties in generating a good prediction model is changing this paradigm to the indication and selection of therapy according to the presence of individual clinical characteristics presaging different responses to any of the respiratory support options. Some of the traditionally accepted risk factors for reintubation (e.g., COPD, obesity, acute or chronic heart failure) have been reported as protective factors when analyzed in populations receiving adequate postextubation therapy [17,18]. In addition, the reduced diagnostic accuracy of clinical models predicting extubation failure includes a low sensitivity or negative predictive value down to 63% and 19% respectively (unpublished data). Thus, clinical trials and meta-analyses reporting benefit of postextubation therapy in patients defined at low risk could be explained in part by the use of preventive therapy on false negative low risk patients [10,16].

Moreover, other mechanisms of benefit not fully understood can be present in patients at actual low risk. A clinical trial comparing conventional oxygen therapy (COT) and high flow nasal cannula (HFNC) in low risk patients according to an 11-factor model [16], reported as secondary outcomes a reduction in the incidence of postextubation respiratory failure and laryngeal edema that could be explained not only by high flow but also the active humidification.

Tolerance to noninvasive ventilation (NIV) is a clinical concern especially in asymptomatic patients planned for preventive therapy. Discomfort leading to intolerance not only reduces time of application and limits the magnitude of applied pressure, but it

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Table 1. Risk factors of post extubation acute respiratory failure

Risk factor	Description	References
Age	>65 years	[5,8,9▪,10–13]
Acute cardiac failure	Cardiac failure as the cause for intubation	[5,10–13]
Chronic cardiac failure	New York Heart Association criteria	[6]
	Left ventricular ejection fraction ≤45%, history of pulmonary edema, ischemic disease, or permanent atrial fibrillation	[8,9▪]
APACHE II score	>12 points the day of extubation	[5,10–13]
Type of weaning	Not simple weaning	[10–13]
	More than one consecutive failure of SBT	[6]
Hypercapnia	After extubation	[6]
	At the end of the SBT	[10–14]
Comorbidity	Charlson score ≥2	[10–13]
	Charlson score ≥2 excluding chronic heart failure	[6]
Secretions management	Airway score 8–12[a]	[6]
	Subjective evaluation of cough reflex or suctioning frequency	[10–13]
Airway patency	Upper airway stridor after extubation	[6]
	Risk for stridor	[10–13]
Chronic lung disease	At least moderate COPD	[10–13]
	COPD, obesity-hypoventilation syndrome, or restrictive pulmonary disease	[8,9▪]
Obesity	BMI >35	[7]
	BMI >30	[8,10–13]
Duration of MV	>7 days	[10–13]

APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation; SBT, spontaneous breathing trial.
[a]Airway score defined as semiquantitative assessment of need for airway care including six categories (e.g., spontaneous cough, gag, sputum quantity, sputum viscosity, suctioning frequency, sputum character), and described by Coplin WM *et al.* [15].

may contribute to anxiety or even panic that can predispose postextubation respiratory failure [11,19▪], as some cases recover after withdrawal of NIV. These are the main reasons for the development of the concept of NIV or oxygen based strategies.

Described options for NIV based strategies include conventional NIV, with optimized interface and pressure settings along with COT during rest periods from NIV, leading to a wide range of application duration, from 4 to 14 h a day [11]. Other options are combined therapy with conventional NIV plus HFNC during rest periods from NIV, expecting around 12 per 24 h of application of NIV mainly during night hours [8], or optimized NIV, including active humidification, aiming to maintain use throughout all the planned period of treatment [12].

One study comparing NIV plus COT with NIV plus HFNC showed reduced dyspnea and tachypnea and greater comfort during breaks using HFNC [20] and it seems reasonable to consider that the greater the predicted extubation failure rate, the greater the effort should be in trying to apply NIV for the maximum possible time. There is evidence for some subgroups of patients benefiting the most with NIV based strategies compared to HFNC (Fig. 1) [8].

Patients at very high risk, defined as those with more than three risk factors selected from the 11-factor model, have been shown to benefit with a 48 h NIV based strategy using optimized NIV compared to HFNC. The reintubation rate in this study was 23.3% vs. 38.8% respectively, the effect size was 15.5% and the time of application of NIV was 22.5 h the first day and 18 h the second. Although HFNC remains more comfortable than humidified NIV, there are conflicting results on the effect of COT vs. HFNC breaks on tolerance to reconnection to NIV in patients using a combined strategy [12,20].

Obese patients at high risk for hypoxemic respiratory failure, defined as those with a maximum of three risk factors selected from the 11-factors model excluding those with hypercapnia at the end of the SBT, presented a nonsignificant but clinically meaningful reduction in the reintubation rate of 9.7%

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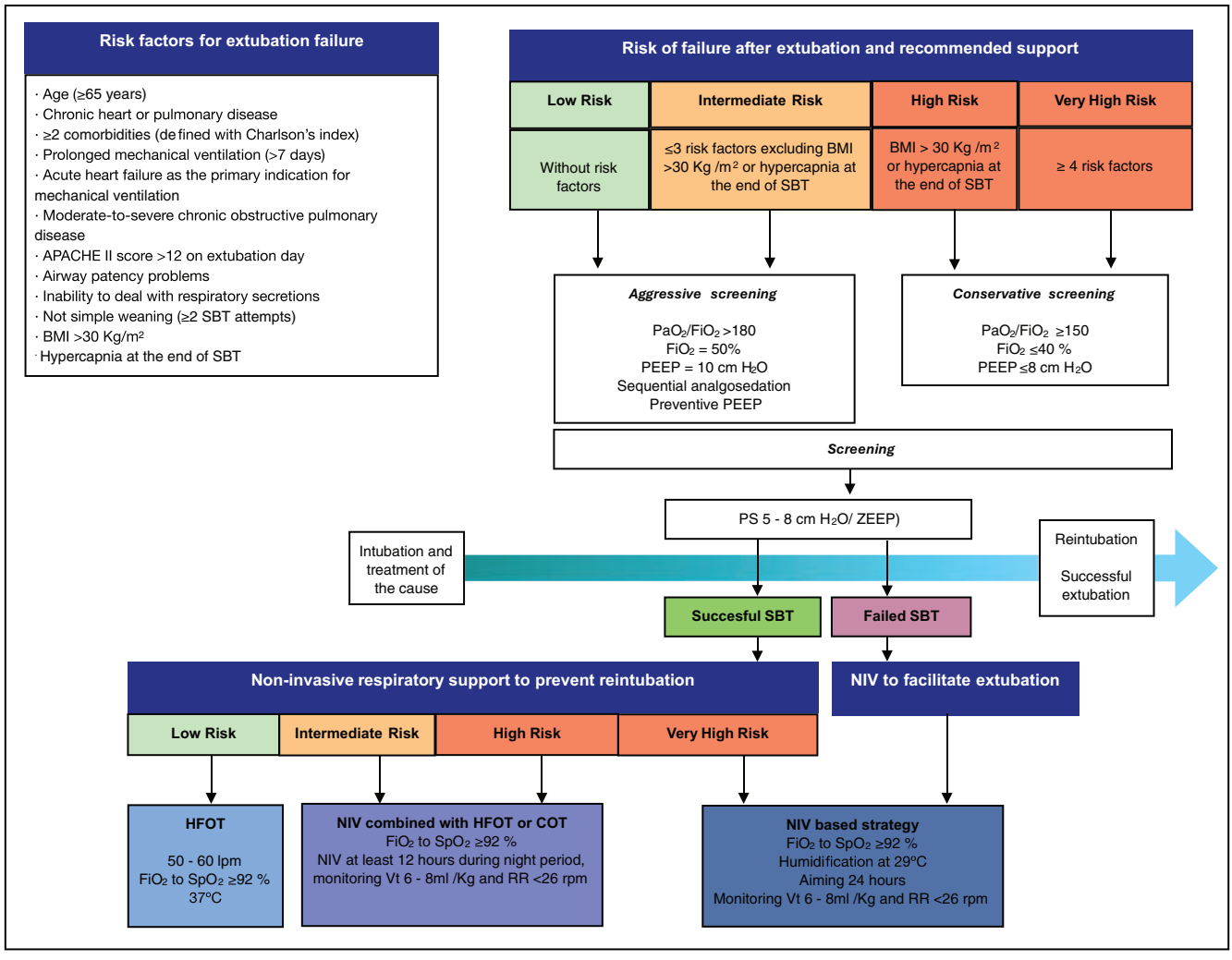
Risk factors for extubation failure
· Age (≥65 years)
· Chronic heart or pulmonary disease
· ≥2 comorbidities (defined with Charlson's index)
· Prolonged mechanical ventilation (>7 days)
· Acute heart failure as the primary indication for mechanical ventilation
· Moderate-to-severe chronic obstructive pulmonary disease
· APACHE II score >12 on extubation day
· Airway patency problems
· Inability to deal with respiratory secretions
· Not simple weaning (≥2 SBT attempts)
· BMI >30 Kg/m²
· Hypercapnia at the end of SBT
Risk of failure after extubation and recommended support
Low Risk
Intermediate Risk
High Risk
Very High Risk
Without risk factors
≤3 risk factors excluding BMI >30 Kg /m² or hypercapnia at the end of SBT
BMI > 30 Kg /m² or hypercapnia at the end of SBT
≥ 4 risk factors
Aggressive screening
PaO2/FiO2 >180
FiO2 = 50%
PEEP = 10 cm H2O
Sequential analgosedation
Preventive PEEP
Conservative screening
PaO2/FiO2 ≥150
FiO2 ≤40 %
PEEP ≤8 cm H2O
Screening
PS 5 - 8 cm H2O/ ZEEP)
Intubation and treatment of the cause
Reintubation
Successful extubation
Succesful SBT
Failed SBT
Non-invasive respiratory support to prevent reintubation
NIV to facilitate extubation
Low Risk
Intermediate Risk
High Risk
Very High Risk
HFOT
50 - 60 lpm
FiO2 to SpO2 ≥92 %
37°C
NIV combined with HFOT or COT
FiO2 to SpO2 ≥92 %
NIV at least 12 hours during night period, monitoring Vt 6 - 8ml /Kg and RR <26 rpm
NIV based strategy
FiO2 to SpO2 ≥92 %
Humidification at 29°C
Aiming 24 hours
Monitoring Vt 6 - 8ml /Kg and RR <26 rpm

FIGURE 1. Proposal to individualize weaning considering individual risk stratification and postextubation support application. BMI, body mass index; HFOT, high-flow oxygen therapy; COT, conventional oxygen therapy; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PS, pressure support; SBT, spontaneous breathing trial. Adapted from Rodriguez P, Hernández G. Weaning from mechanical ventilation: speed it up and make it safe. Med Intensiva (Engl Ed). 2024;48:356–9. doi:10.1016/j.medine.2024.03.003.

(23.6% vs. 33.3% respectively) after 48 h of optimized NIV compared to HFNC. This subgroup of patients tolerates NIV well, with a median of 24 h of application the first day and 19 the second, similar to the HFNC group [13]. However, there is a risk that this study lacks adequate statistical power. The most important safety concern related to postextubation noninvasive support therapies is the risk of delaying a needed reintubation, possibly increasing the mortality rate [21]. Interestingly, neither these obese patients at risk for hypoxemic failure nor those at very high risk presented any difference in time to reintubation or difference in mortality rate.

In the case of a general population of obese patients including those with obstructive sleep apnea at risk for hypercapnic failure, there are some additional results supporting the benefit of a NIV based strategy. First, a large pragmatic randomized trial comparing a NIV based strategy vs. an oxygen based strategy including COT and HFNC reported that the NIV based strategy reduced the need for escalation of therapy [19▪], and a posthoc cross-over analysis showed a reduced reintubation rate from 13% to 9% using the NIV based strategy. Second, a posthoc analysis by Thille *et al.* [22], reported that a NIV based strategy combined with HFNC compared to HFNC alone reduced the reintubation rate in patients with a body mass index (BMI) ≥30 from 18% to 6%, and with overweight (BMI ≥25) from 21% to 9%.

The fourth subgroup of patients benefiting from a postextubation NIV based strategy is those at risk

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for hypercapnic respiratory failure, defined as those with $pCO_2 \geq 45$ mmHg at the end of the SBT. The benefit of a NIV based strategy in this population was first described by Ferrer *et al.* [14], before availability of HFNC. They found a decrease in the rate of respiratory failure and an improvement in 90-day survival rate compared with COT, without a significant reduction in the reintubation rate (11% vs. 19%, respectively). More recently, a NIV based strategy combined with HFNC was compared to HFNC alone in a posthoc analysis of a large randomized trial including high risk patients selected by the 3-factor model. Although the original trial reported a significant reduction in the reintubation rate, this effect was largely explained by BMI ≥ 25 and the presence of hypercapnia at the end of the SBT, with an effect size in hypercapnic patients of 13% (reintubation rates 8% vs. 21%) [8,22].

Patients at high risk according to any of the prediction models not fulfilling criteria for the previous subgroups could receive both a NIV based strategy or HFNC prevention:

On one hand, the use of HFNC in high risk patients is supported by a large noninferiority randomized trial comparing a protocol including a fixed 24 h period of conventional NIV or HFNC. In this study, NIV was optimized with total face mask, obtaining 14 h of application. This protocol led to some cases of postextubation respiratory failure due to the NIV therapy itself, and noninferiority criteria were fulfilled with reintubation rates at 72 h of 19% and 23%, respectively [11].

On the other hand, another large randomized trial of ICU patients at high risk of extubation failure showed that 7 days reintubation rate was lower (12%) with a NIV strategy consisting of a combination of HFNC and conventional NIV applied immediately after extubation than HFNC alone (18%) ($P = 0.02$). Enrollees received at least 48 h of preventive treatment, but continuation of prevention depended on the clinical condition and was discontinued upon complete respiratory recovery. [8].

This dilemma of using a NIV strategy vs. HFNC alone for patients at high risk of extubation failure cannot be answered with a simple yes or no response. There are many variables modifying the optimal therapy chosen for a single patient, including local practices, availability of preventive devices, diagnosis of ICU-acquired delirium or other factors limiting NIV's tolerance, patient's preference, etc.

In addition, two new variables increase the confusion for decision making. First, the definition of reintubation has traditionally been defined as occurring ≤ 72 h from extubation, but ever since postextubation respiratory support has become a standard of care in many intensive care units, most experts suggest that it should be increased. It has been widely accepted that when postextubation support is applied, reintubation should be defined as occurring within 7 days, but time on postextubation support and type of support, could redefine this new definition. Hernandez *et al.* [11,12] reported delayed reintubation episodes in patients receiving 24 or 48 h of HFNC therapy compared to a NIV based strategy, and an exploratory analysis performed in patients receiving 48 h of prevention after extubation and defining reintubation as occurring within 5 days of extubation, resulted in a lack of statistical significance. How reintubation is defined should be considered when analyzing results from clinical trials.

The second variable is that the continuation of noninvasive support after the planned prevention period to treat residual postextubation respiratory failure can further improve outcomes.

SETTING POSTEXTUBATION RESPIRATORY SUPPORT ACCORDING TO CLINICAL CONDITION

Setting postextubation respiratory support according to clinical condition aims to individualize treatment of postextubation respiratory failure to avoid reintubation. Pure preventive protocols including fixed periods of application of postextubation noninvasive respiratory support are scarce [10,11]. Most trials allow prolonging respiratory support until complete recovery in patients with persistent mild hypoxemia [8,24]. It is not clear whether or not this approach further reduces reintubation compared to fixed preventive time but increasing time of respiratory support seems to improve outcomes. For example, Maggiore *et al.* [24] demonstrated increased benefit after 24 h of application of HFNC in terms of oxygenation and respiratory frequency. Also, there are delayed reintubations after HFNC withdrawal not observed in patients with NIV based strategies [12,17]. Furthermore, protocols allowing withdrawal of respiratory support before 24 h in patients without early postextubation respiratory failure can reduce effectiveness of prevention in patients with delayed failure [24,25].

Other protocols further include escalation of therapy in patients with respiratory deterioration, but treatment of established postextubation respiratory failure remains controversial since Esteban *et al.* [21] reported lack of benefit and a risk for increased mortality in a study comparing NIV to COT in a cohort at high risk for extubation failure. However it is worth mentioning that this study extubated patients after a very conservative screening including a $PaO_2/FiO_2 > 150$ on $FiO_2 \leq 40\%$ and

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PEEP $\leq$5 cmH_2O and the hypoxemic inclusion criteria required a $PaO_2 < 80$ mmHg on FiO_2 >50%, favoring selection of patients with severe respiratory deterioration.

Maggiore *et al.* [23] have also explored early postextubation respiratory support in cases with mild hypoxemia defined as pO_2/FiO_2 <300 on FiO_2 31% within the first two hours after extubation. They randomized patients to HFNC or COT, allowing prolonged support, escalation of therapy and early withdrawal. Patients were extubated after using a very conservative screening criterion and 19.4% were excluded because they did not meet postextubation hypoxemic criteria, thus assuring that only very mild cases were included. Both groups had relatively low reintubation rates (13% in HFNC and 11% in venturimask) ($P = 0.49$) probably reflecting their relatively mild severity of hypoxemic respiratory failure (PaO_2/FiO_2 approximately 230 in both groups). Fewer patients in the HFNC (8% vs. 17%) ($P = 0.002$) were escalated to NIV as per the protocol, but without differences in intubation rate or mortality, the clinical importance of this is debatable.

A summary of studies commented for both indications is presented in Table 2.

POSTEXTUBATION RESPIRATORY SUPPORT ACCORDING TO TIMING OF EXTUBATION

Planning postextubation respiratory support according to timing of extubation aims to facilitate extubation to reduce the time on invasive MV. A systematic review on early extubation facilitated by NIV has proven benefits like reduced rates of death and pneumonia, without increasing the risk of weaning failure or reintubation and those benefits, mainly reduced mortality, are greater in patients with COPD [26]. Most of those trials were performed around two decades ago, including patients not tolerating SBTs prior to extubation. However, many of those trials included patients failing highly demanding SBTs (e.g., prolonged T-tube trials) performed after delayed screening (e.g., pO_2/FiO_2 ratio $\geq$150 mmHg whereas on PEEP $\leq$5 cmH_2O or pO_2/FiO_2 ratio $\geq$200 mmHg while on PEEP 8 cmH_2O).

After 2007 [1], accepted screening tests used earlier definition to start liberation from MV, including PaO_2/FiO_2 ratio $\geq$150 mmHg while on FiO_2 $\leq$40% and PEEP $\leq$8 cmH_2O, and thereafter even earlier with PaO_2/FiO_2 ratio $\geq$180 mmHg while on FiO2 $\leq$50% and PEEP $\leq$10 cmH_2O [27]. Guidelines published in 2017 [28] and trials ever since [9▪,29] recommend performing easier SBTs with low level pressure support up to 8 cmH_2O. Thus, criteria used to define early or facilitated extubation have dramatically changed during the past decade. Perkins *et al.* [27] using earlier screening criteria, randomized 319 patients who failed a SBT to early extubation and NIV or continued invasive ventilation and extubation according to standard criteria once they passed a SBT. The main outcome variable, time from randomization to liberation from all forms of ventilator was 4.3 days in the early NIV

Table 2. Design and results of randomized trials comparing different noninvasive respiratory support strategies to prevent extubation failure

Trial	Design				Results	
	n	Risk	Groups	Therapy	Reintubation	ICU stay
Ferrer, 2005	162	High	NIV vs. COT	24 h	11% vs. 22%	11 (±8) vs. 13 (±11)
Nava, 2005	97	High	NIV vs. COT	48 h	8% vs. 24%	9 (±6) vs. 12 (±21)
Ferrer, 2009	106	Hypercapnic	NIV vs. COT	24 h	11% vs. 19%	11 (±13) vs. 10 (±9)
Maggiore, 2014	105	Hypoxemic	HFNC vs. COT	≥48 h	3.8% vs. 21.2%	12 (±10) vs. 10 (±8)
Hernandez, 2016	527	Low	HFNC vs. COT	24 h	4.9% vs. 12.2%	6 (2–8) vs. 6 (2–9)
Hernandez, 2016	604	High	NIV vs. HFNC	24 h	19.1% vs. 22.8%	4 (2–9) vs. 3 (2–7)
Thille, 2019	648	High	HFNC vs. NIV+HFNC	≥48 h	18% vs. 12%	11 (7–19) vs. 12 (7–19)
Maggiore, 2022	494	Hypoxemic	HFNC vs. COT	≥24 h	13% vs. 11%	11 (7–21) vs. 11 (7–20)
Hernandez, 2022	182	Very high	Humidified NIV vs. HFNC	48 h	22.8% vs. 38.9%	9 (4–15) vs. 12 (7–19)
De Jong, 2023	981	Obese	NIV vs. Oxygen based strategies	≥24 h	14% vs. 16%	7 (±7) vs. 7 (±7)
Hernandez, 2024	144	Obese	Humidified NIV vs. HFNC	48 h	23.6% vs. 33.3%	11 (6–20) vs. 6 (3–17)

COT, conventional oxygen therapy; HFNC, high flow nasal cannula; NIV, noninvasive ventilation.

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group and 4.5 days in the standard care group ($P = \text{NS}$) and there were no differences in reintubation, tracheostomy rates or survival. Although this trial did not find that early NIV reduced time to liberation, notable observations include that 75% of eligible patients succeeded the initial SBT after earlier screening, suggesting that there is room to accelerate extubation using this screening approach. Also, time on invasive ventilation was shortened with the early NIV approach, resulting in less antibiotic usage for presumed respiratory infection and avoidance of other complications related to longer duration on invasive ventilation.

Recently the early screening approach was confirmed to hasten extubation in low to intermediate risk patients, defined as those with ≤ 3 risk factors, excluding those likely to benefit from a NIV based strategy (e.g., obese, hypercapnic at the end of the SBT) and with planned HFNC prevention [30▪▪]. The reason for analyzing this subset of patients was to avoid the bias of differences in time of application of NIV that could have led to variations in the reintubation rate. However, it seems that the concept of early extubation will change to using the new screening and SBT definition, while planning optimized NIV based strategies after extubation. It is noteworthy that when earlier screening ($PaO_2/FiO_2 > 180$ and PEEP 10 cmH_2O) was combined with the easier SBT (pressure support 8 cmH_2O + PEEP 5 cmH_2O) the weaning success rate was only 45.7% and this subgroup was discontinued at the interim analysis for safety reasons.

CONCLUSION

Although predicting risk for failing extubation is a clinical challenge, planning postextubation respiratory support must consider not only the predicted risk but also clinical conditions that may favor a NIV based strategy, such as obesity or hypercapnia at the end of a SBT. Nonetheless, even low risk patients may benefit from postextubation support, perhaps because of favorable effects of heat and humidification on mucociliary function or upper airway endotracheal tube trauma. Technological advances have enhanced both the advantages and complexity of the therapeutic arsenal and has moved the decision making beyond HFNC vs. NIV. There is increasing evidence that extubation can be safely accelerated just by modifying aggressiveness of screening for an SBT, and appropriate use of postextubation noninvasive respiratory support still holds promise for improving postextubation outcomes.

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- ▪ of special interest
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Randomized trial comparing for the first time different options of respiratory screening criteria and SBTs on pressure support that demonstrates that extubation can be accelerated without increasing risks for the patients.

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